UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/931,007	08/17/2001	Daniel Scherman	03806-0512	2754

7590 07/23/2003

Finnegan, Henderson, Farabow,
Garrett & Dunner, L.L.P.
1300 I Street, N. W.
Washington, DC 20005-3315

EXAMINER	
SHUKLA, RAM R	
ART UNIT	**PAPER NUMBER**
1632	13

DATE MAILED: 07/23/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/931,007	SCHERMAN ET AL.	
	Examiner	Art Unit	
	Ram R. Shukla	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 April 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-83 and 101-112* is/are pending in the application.

4a) Of the above claim(s) *8,19,29,32-37,40,46-82 and 101-112* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-7,9-18,20-28,30-39 and 41-45* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☒ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

1. Applicant's election with traverse of group I, claims 1-7, 9-18, 20-28, 30-39, 41-45 and 83-100 in Paper No. 12 is acknowledged. The traversal is on the ground(s) that the office has not shown search burden and that the inventions are classified in the same class and subclass. This is not found persuasive because the restriction requirement is not only based on search burden and classification of invention in a certain class/subclass does not mean that the inventions are not distinct and will not require separate searches. For example, class 424, subclass 93.1 contains all the inventions directed to whole live microorganism, cell or virus and searching class 424 subclass 93.1 will not be sufficient for considering these inventions. Regarding the issue of search burden, it is noted that there will be serious search burden for searching all the different inventions because as discussed in the previous office action, they require compositions with different structure, function and utilities, different carriers and different organisms and searches for all these inventions will not be coextensive.

The requirement is still deemed proper and is therefore made FINAL.

2. Applicants' election of an antisense RNA as the inhibitory transcript and physical/mechanical method of introducing nucleic acid into target tissue or cell as species is also acknowledged.

3. It is noted that applicants have drawn office's attention to omission of claim 19 from the restriction requirement. This inadvertent error is regretted and it is noted that claim 19 is included in group I since recites that the inhibitory transcript is a ribozyme. Since the elected species is antisense RNA, claim 19 is withdrawn from consideration. Claims 33-37 are withdrawn from further consideration because they are drawn to non elected species.

4. Claims 8, 29, 40, 46-82 and 101-112 have been withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in Paper No. 12.

5. Claims 83-100 have been cancelled.

6. Claims 1-7, 9-18, 20-28, 30-39 and 41-45 are under consideration.

7. Acknowledgment is made of applicant's claim for foreign priority based on an application filed in France 001/10730 on 08/18/2000. It is noted, however, that applicant has not filed a certified copy of the above mentioned application as required by 35 U.S.C. 119(b).

Claim Rejections - 35 USC § 112

8. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

9. Claim 1-7, 9-18, 20-28, 30-39 and 41-45 rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

While determining whether a specification is enabling, one considers whether the claimed invention provides sufficient guidance to make and use the claimed invention, if not, whether an artisan would have required undue experimentation to make and use the claimed invention and whether working examples have been provided. When determining whether a specification meets the enablement requirements, some of the factors that need to be analyzed are: the breadth of the claims, the nature of the invention, the state of the prior art, the level of one of ordinary skill, the level of predictability in the art, the amount of direction provided by the inventor, the existence of working examples, and whether the quantity of any necessary experimentation to make or use the invention based on the content of the disclosure is "undue" (In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)). Furthermore, USPTO does not have laboratory facilities to

test if an invention will function as claimed when working examples are not disclosed in the specification, therefore, enablement issues are raised and discussed based on the state of knowledge pertinent to an art at the time of the invention, therefore skepticism raised in the enablement rejections are those raised in the art by artisans of expertise.

Claimed invention is drawn to an in vivo method of regulating expression of a transgene of interest by simultaneously introducing in a tissue or cell a first nucleic acid and a second nucleic acid wherein the first nucleic acid comprises the transgene of interest encoding the transcript of interest whereas the second transgene encodes an inhibitory transcript, coexpressing said nucleic acids in the target tissue or cell to inhibit the activity of the transcript of interest with the inhibitory transcript. Dependent claims recite the nature of the transgene of interest and method of introducing the nucleic acids etc.

The specification is not enabling for the claimed invention because (i) the method of targeting a nucleic acid to any tissue or any cell in vivo is unpredicatable (ii) the in vivo inhibition of a gene of interest using antisense transcript is unpredictable and the specification as filed does not provide sufficient guidance to practice the claimed method in vivo. An artisan of skill would have required experimentation to make and use the claimed invention because of the unpredictability of the art of targeted gene delivery and of the art of in vivo inhibition of gene expression using antisense transcript and lack of guidance in the specification to address the issues of unpredictability and other considerations as discussed below.

While progress has been made in recent years for *in vivo* gene transfer, vector targeting *in vivo* to desired organs continues to be unpredictable and inefficient. This is supported by numerous teachings available in the art. For example, Deonarain (Deonarain MP. Exp. Opin. Ther. Patents 8(1)53-69, 1998) is a 1998 publication which indicates that one of the biggest problems hampering successful gene therapy is the "ability to target a gene to a significant population of cells and express it at adequate levels for a long enough period of time" (page 53, first paragraph). Deonarain reviews new techniques under experimentation in the

art which show promise, but is currently even less efficient than viral gene delivery (see page 65, first paragraph under Conclusion section). While applicant's specification supports in vitro expression, the specification fails to teach one of skill in the art how to overcome the unpredictability for vector targeting such that efficient gene transfer is achieved by any mode of delivery. The specification fails to teach any specific targeting techniques, fails to provide any working examples which encompass vector targeting, and fails to direct the skilled artisan to any teachings of targeting strategies known in the art which would allow one of skill in the art to practice the claimed invention without undue experimentation. It is emphasized that the method as recited could be practiced by introducing two vectors comprising the first and second nucleic acids respectively or both the nucleic acids could be present on one vector. While the expression of two transcripts from one vector could provide the two transcripts at one location in a cell or a tissue, the expression of the two transcripts from two different vectors at one location and in sufficient levels to effect gene expression inhibition could not be predicted. Regarding claims wherein an agent is administered to the animal for regulating the activity or expression of the inhibitory transcript or the transcript of interest, the specification does not as to how the agent will be targeted to the tissue or cell. Regarding the claims that recite that the transgene of interest corrects genetic abnormality or deficiency or has therapeutic activity, the specification does not provide any guidance as to how to target the transgene to the target tissue and what amounts or levels of the transgene transcript will be required to correct or treat a genetic abnormality or disease.

The art of antisense therapy is highly unpredictable. Branch (TIBS, February 1998 Vol. 23, pages 45-50) reviewed the state of the antisense art and noted: "Antisense molecules and ribozymes capture the imagination with their promise or rational drug design and exquisite specificity. However, they are far more difficult to produce than was originally anticipated, and their ability to eliminate the function of a single gene has never been proven."; "To minimize unwanted non-antisense effects, investigators are searching for antisense compounds and ribozymes whose targets sites are particularly vulnerable to attack. This is a challenging quest.";

"However, their unpredictability confounds research application of nucleic acid reagents."; "Non-antisense effects are not the only impediments to rational antisense drug design. The internal structures of target RNAs and their associations with cellular proteins create physical barriers, which render most potential binding sites inaccessible to antisense molecules."; "Years of investigation can be required to figure out what an 'antisense' molecule is actually doing,..."; "Because knowledge of their underlying mechanism is typically acting, non-antisense effects muddy the waters."; "Because biologically active compounds generally have a variety of effects, dose-response curves are always needed to establish a compounds primary pharmacological identity. Antisense compounds are no exception. As is true of all pharmaceuticals, the value of a potential antisense drug can only be judged after its intended clinical use is known, and quantitative information about its dose-response curve of conventional drugs, which typically span two to three orders of magnitude, those of antisense drugs, extend only across a narrow concentration range."; "Because it is very difficult to predict what portions of an RNA molecule will be accessible *in vivo*, effective antisense molecules must be determined empirically by screening large number of candidates for their ability to act inside cells."; "Binding is the rare exception rather than the rule, and antisense molecules are excluded from most complementary sites. Since accessibility cannot be predicted, rational design of antisense molecules in not possible."; and, "The relationship between accessibility to oligonucleotide (ODN) binding and vulnerability to ODN-mediated antisense inhibition *in vivo* is beginning to be explored...It is not yet clear whether *in vitro* screening techniques...will identify ODN's that are effective *in vivo*."

Jen et al. (Stem Cells, 2000, Vol. 18:307-319) discuss antisense-based therapy and the challenges that remain before the use of antisense becomes routine in a therapeutic setting. The authors conclude, "Given the state of the art, it is perhaps not surprising that effective and efficient clinical translation of the antisense strategy has remained elusive." It is also stated, "The key challenges to this field have been outlined above. It is clear that they will have to be solved if this approach to specific antitumor therapy is to become a useful treatment

approach. A large number of diverse and talented groups are working on this problem, and we can all hope that their efforts will help lead to establishment of this promising form of therapy."

Dias et al. (European Journal of Pharmaceutics and Biopharmaceutics, 2002 Vol. 54:263-269) addresses the limitations of antisense-based therapy. Dias et al. state, "Even though the antisense strategy is widely employed currently, it has certain defined limitations. Although it is relatively easy to synthesize phosphodiester oligonucleotides, these cannot *[emphasis added]* be used as drugs due to their propensity to be easily degraded by cellular nucleases" (see page 263, first column). Dias et al. further discuss that different methods, such as electroporation, microinjection or the binding to particular peptides with membrane translocation properties have been developed to overcome internalization problems, however these methods are easily applied in cultured cells, but may or may not be useful in *in vivo* systems (see page 263, second column).

In conclusion, the art of antisense therapy is highly unpredictable and the specification has failed to provide sufficient guidance as to how would an artisan have dealt with the art recognized issues such as those listed above and therefore it would have required undue experimentation for an artisan to have successfully practiced the claimed invention with a reasonable expectation of success.

10. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

11. Claims 38 and 39 rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 38 and 39 are indefinite because they recite that the target tissue is of human origin. Since, the independent claim, claim 1 is directed to "a target nonhuman animal tissue or cell", how can it be a human tissue or cell.

12. No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ram R. Shukla whose telephone number is (703) 305-1677. The examiner can normally be reached on Monday through Friday from 7:30 am to 4:00 p.m. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah Reynolds, can be reached on (703) 305-4051. The fax phone number for this Group is (703) 308-4242. The after-final fax number is (703) 87209307. Any inquiry of a general nature, formal matters or relating to the status of this application or proceeding should be directed to the William Phillips whose telephone number is (703) 305-3413.

RAM SHUKLA
PRIMARY EXAMINER

Ram R. Shukla, Ph.D.
Primary Examiner
Art Unit 1632